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Cancer Stem Cells: A New Way To Look at an Old Disease

by Jaime Modiano, VMD, PhD; University of Minnesota

Cancer and Public Health. Undoubtedly, cancer is among the conditions that will have the most significant impact on the health and well being of people and their pets during the 21st century. The entity that is cancer has been recognized since the times of the ancient Greeks, but it was only in the latter part of the 20th century that we began to understand why cancer happens. As the art and science of medicine and veterinary medicine reduced morbidity and mortality from other causes and the expected lifespan increased, cancer became more prevalent in the human and canine populations. Today, cancer is the leading cause of death in people under the age of 85, and it is the most common cause of disease-related death in dogs. It is estimated that 30% of people and dogs will get cancer in their lifetime, and in dogs, more than half of those affected will die from their disease.

Despite these grim statistics, we cannot ignore advances that we have achieved in diagnosis and treatment of cancer. With proper standard of care, cancer patients can reasonably expect to add at least 10% of a lifetime after their diagnosis and many patients survive cancer and lead normal, productive and healthy lives. Because cures are difficult to define, the treatment goal today is to make cancer a manageable chronic disease. Improved application of existing therapies (surgery, chemotherapy, and radiation), as well as new therapies coming on line can achieve this for a large number of patients. However, sometimes the price is too high - either because the side effects are unacceptable or because the treatment is cost prohibitive. Both of these are greater obstacles in veterinary medicine, where quality of life is paramount and where health care reimbursements from insurance are not the norm. It is this segment of the population, then, that most preoccupies us and fuels our desire to continue probing the inner workings of cancer so that we can realistically design better strategies to prevent, diagnose, and treat this condition.

Cancer as a Disease of Stem Cells. With that background, we can appreciate the importance of thinking outside the box. What if we ask questions about why we fail so often, as opposed to trying to incrementally build on small gains? It is this type of thinking that has led to a revised theory about the origins of cancer that may revolutionize how we approach this disease.

For >40 years we have known that cancers arise from a single cell (clonal expansion) and that a series of mutations are necessary for the cell of origin to acquire the malignant phenotype. However, the dominant theory assumed that all cells possessed an equal capacity for self-renewal (see below for definition). It also assumed that proliferation was a stochastic ("random") process driven entirely by environmental selection of favorable mutations. However, self-renewal and differentiation potential are the key elements that define what a stem cell is. So a competing theory now exists whose main tenet is that cancer is a consequence of malignant transformation of cells that retain properties of stem cells, but harbor defined mutations that endow them with malignant properties. It is not entirely a different concept, but simply a different way of looking at the same data and it is intellectually satis-

fying because it explains much about cancer that was difficult to reconcile with the old models.

What is a Cancer Stem Cell? The first and most important thing to note is that normal stem cells, such as those harvested for regenerative therapies are!!!!! the same as cancer stem cells. The American Association for Cancer Research (AACR) convened a Workshop in February, 2006 to achieve a consensus definition of a cancer stem cell. Based on that workshop, the consensus definition was *"a cell within a tumor that possesses the capacity to self-renew and to cause the heterogeneous lineages of cancer cells that comprise the tumor."* For this reason, it is important to define cancer stem cells based on their ability to recapitulate a continuously growing tumor. In essence, this means a tumor that can be serially passaged *in vivo* (in a laboratory mouse) by one (or very few) cell(s), and thus the term in its strictest definition is synonymous with "tumor- initiating cell" or "tumorigenic cell". The term "cancer stem cell" is somewhat unfortunate as it can easily be interpreted mean that such cells derive from stem cells of the corresponding tissue. In fact, cancer stem cells may indeed arise from normal stem cells by mutations that make them cancerous, but this may not be the case in all tumors. That is, it is possible that more differentiated cells can acquire the capacity for self-renewal and become immortalized through multiple mutations, so it is this differentiated cell, and not the tissue stem cell, that eventually evolves to become a full-blown cancer stem cell.

It is important to note that proliferation is not the same as self-renewal. A self-renewing cell division results in one or both daughter cells (progeny) that have essentially the same ability to replicate and generate differentiated cell lineages as the progenitor cell. Stem cells can undergo symmetrical self-renewing division, causing identical daughter cells that retain "sternness" or self-renewal capacity, or asymmetrical self-renewing division, resulting in one stem cell and one more differentiated progenitor cell that can continue along a defined lineage or lineages. It also is possible that some stem cells may divide symmetrically to form two progenitor cells, leading to stem cell depletion. Promoting this latter form of division would be a way to deplete the cancer stem cell population by differentiation, and may hence constitute an alternative strategy to inducing cell death to treat cancer.

Do Cancer Stem Cells Really Exist? The existence of cancer stem cells is now documented; they are characterized by peculiar phenotypes, by defined sets of genetic mutations, and by their ability to form tumors that can be serially passaged in laboratory animals. In the case of lymphoma or leukemia, <1 in 250,000 tumor cells has the properties that define a cancer stem cell. Similar results have been obtained for a variety of solid, tumors, although much work remains to be done to define the "cancer stem cell" for many types of cancer.

Clinical Implications of Cancer Stem Cells. The cancer stem cell model can explain various paradoxical findings regarding tumors and their natural history. It accounts for the relatively small number of genes that are disproportionately associated with a multitude of cancers, for the ability of multicellular organisms (like people and dogs) to reach reproductive age and attain

long lives without cancer, and perhaps most importantly, for the observed nature of tumor relapse and metastasis. Cancer stem cells divide infrequently and are thus resistant to most of the types of treatments we use for cancer (which rely on killing rapidly dividing cells). Even though they divide rarely, cancer stem cells have the potential to regenerate the full complement of progeny that originally comprised the tumor. Thus, failure to eliminate cancer stem cells with - or after cessation of - chemotherapy sets the stage for tumor re-growth and relapse, which would not occur if the surviving cells lacked the capacity for self-renewal). The acquisition of additional mutations, possibly due to the therapy itself, allows the remaining cancer stem cells to generate new progeny with enhanced survivability in novel environments, favoring aggressive, metastatic phenotypes. This suggests that, in order to achieve sustained remissions, we will need to devise treatment regimens that target the cancer stem cell compartment.

Cancer Stem Cells and Canine Tumors. The stem cell theory of cancer has not been conclusively proven in dogs, but we have seen subpopulations of cells in hemangiosarcoma and in lymphoma that have phenotypes consistent with stem cell origin. For hemangiosarcoma, we extended these observations to define a phenotype that firmly established the bone marrow origin of this tumor, and allowed us to distinguish hemangiosarcoma cells from other bone marrow-derived cells and from normal circulating endothelial cells. This led to the development of a useful diagnostic test for hemangiosarcoma. More recently, we have shown that the tumors harbor specific subpopulations that retain the "primitive" (stem cell-like) characteristics and may harbor unique gene expression signatures. In fact, the relative frequency of these cells may explain the observed differences in the clinical behavior of these tumors. Our current work focuses on defining these cancer stem cell populations and their usefulness to predict responses to standard of care, as well as to identify new treatments to

effectively target these cells. The premise that appropriate activation of the immune system might be able to eliminate both the cancer stem cells and their progeny is among the concepts that we plan to explore in an ongoing clinical trial for osteosarcoma that is supported jointly by the NCI and the AKC CHF.

Biographical Profile

Dr. Jaime Modiano hails from Mexico City, where he graduated from the baccalaureate program at Colegio Columbia. He did undergraduate work in Biomedical Sciences at Texas A&M University in College Station, TX for three years before moving on to veterinary school at the University of Pennsylvania. He completed his veterinary training and PhD in Immunology at Penn, followed by a residency in Veterinary Clinical Pathology at Colorado State University, and a post-doctoral fellowship at the National Jewish Center for Immunology and Respiratory Medicine in Denver, CO. He was appointed to the faculty in the Department of Veterinary Pathobiology at Texas A&M University as Assistant Professor between 1995 and 1999. Dr. Modiano returned to Denver from 1999 to 2007; there, he held Scientist and Senior Scientist appointments at the AMC Cancer Research Center and he was Associate Professor of Immunology and Full Member of the Cancer Center at the School of Medicine of the University of Colorado Health Sciences Center. In July of 2007, Dr. Modiano joined the College of Veterinary Medicine, School of Medicine, and Comprehensive Cancer Center at the University of Minnesota, where he continues his research program as Professor of Comparative Oncology holding the Al and June Perlman Endowed Chair.

Between 2001 and 2003, Dr. Modiano served as Director of Cancer Immunology and Immunotherapy for the Donald Monk Cancer Research Foundation; he also is a partner at Veterinary Research Associates, LLP, a company focused on development and implementation of diagnostics for veterinary medicine and a founder/scientist at ApopLogic Pharmaceuticals, LLC, a biotechnology company focused on development of cancer therapeutics. His research program has had uninterrupted support from federal and private sources for 13 years, leading to co-authorship of more than 50 peer-reviewed scientific manuscripts, and ~200 abstracts, presentations, and book chapters focused on various aspects of immunology, cancer cell biology, the genetic basis of cancer and applications of gene therapy.

Dr. Modiano is married to Dr. Michelle Ritt, a board certified specialist in Veterinary Internal Medicine. They share their home with Logan, a champion agility Gordon setter and Quetzal, a German Shepherd Dog.

Dr. Modiano 's research has been supported by the following grants.

1626T: Significance of Tumor Suppressor Genes in Canine Cancer

2254A: Heritable and Sporadic Genetic Lesions in Canine Lymphoma and Osteosarcoma 615A-T: Heritable and Sporadic Genetic Lesions in Canine Lymphoma

SO YOU WANT TO BREED SCHIPPERKES

by Virginia Larioza *(originally published in the AKC Gazette March 2004*)

The other day I had an inquiry via email. Any one who is known as a “dog breeder” these days receives these. It was cute actually…a young woman (I guessed maybe late teens because she mentioned having been in 4-H rabbit projects for 8 years) and her “little” brother have a wonderful pet (female) Schipperke. The family raises Labs and would like to start “a Schipperke breeding program.” After the initial roll of the eyes and the silent “Oh Lord” I answered her. I have taken the time over the years to answer each and every phone call (it used to be mostly that) and now emails of this nature with politeness, respect and information. After all, everyone who eventually breeds good dogs starts somewhere. Usually these folks are motivated by a love of their own dog and the breed. They honestly don’t know what is involved. Few are motivated by money; I believe if they were they would be starting with a more expensive breed than Schips. If you can take the time to lay out facts (including the money side for those who might be interesting in making a little extra money from Skippy) I have found most breeder hopefuls can either be stopped or headed in the right direction towards sincerely learning. I decided once and for all to keep this response and have it on hand to use as a somewhat standard answer to such inquiries in the future.

Thanks for your inquiry. I only sell my puppies on spay/neuter agreements. If I feel a dog is nice enough to be used for breeding it must also finish its AKC championship, and those dogs I sell only on co-ownership.

Unlike most Labs, Schipperkes are not an easy breed to "breed" They often require C-sections (which are usually around $500) and frequently have only one or two puppies. Some are poor milk producers and the puppies need to be tube fed because they are so small (3 to 4 oz. at

birth), which is dangerous and would be hard for you to do as often as needed when you are working or in school.

Tail docking can run from about $25 to $50 a puppy.

From a business stand point Schipperkes are not great sellers. They are not a very well known breed. Additionally because they have strong personalities, are runners, can be aggressive if not well bred and properly socialized etc. the homes/buyers must be really well screened.

We have a very active rescue group here in Michigan and some years have rescued 50 or more Schipperkes. I am sure as a responsible person you understand the need to do the best by this breed. Being a good breeder takes a lot more than just putting a male and female together and having puppies. There are plenty of pet Ships and other dogs around who need homes. A good breeder doesn't just breed dogs... he or she seeks to improve the breed always. This means taking in to account temperament and health issues as well as coat, overall structure, movement, earset etc.

Have you ever read the breed standard?

Are you clear on the proper movement?

Additionally have you researched our genetic heath issues? We have a recently discovered inherited disease (MPSIIIB - you can look it up at www.AKC.org, and all breeding stock must be tested. That test is $75 per dog. We test for Thyroid problems (about $60 plus the office visit) eye diseases (if you can catch a clinic at a dog show this test runs about $25) OFA hips and patella's that runs about $150 to $200. So, I tell any one who wants to breed (not counting the price of the dog) to have at least $1000 set aside. Oh, I forgot you'll have to have extra money to advertise your puppies as unless you belong to the local and National club no one will know who you are, or that you are a breeder. The newspaper is pretty expensive too. Even websites charge for listings, I think the one you found me on is $35 per year. As far as the dog, I have some top winning (Nationally ranked) Schips and many specialty winners, so my standards and prices are high. If I feel a home is right my show dogs start at X amount -- again that is on a co-ownership (so in essence you can't make a move without my approval) and I require the dog be shown to his championship (show entry fees average $22 each day, plus you will have travel expenses) I believe the old saying is… an easy to finish champion (one that is trained, in top condition and mature, also this is assuming you know how to show and groom well enough to compete successfully) is $100 a point. It takes 15 points to finish an AKC champion.

So, as you can see starting a good Schipperke breeding program can be a daunting task. Before you undertake these plans I hope you'll do more research and talk with other breeders.

Ok so now I've shared my two cents. I hope it may help some of you answer inquiries for stud services, or dogs to breed. And I sincerely hope it will help those of you who are not breeders understand where breeders are coming from when you ask them about starting a breeding program of your own. Actually the answers are even more complicated when it comes to time and costs (emotional and financial) involved in breeding good dogs.

I spoke with some other breeders about their ideas on this subject. Why do we raise our hackles when someone asks about breeding their beloved dog? Do we fear competition? Do we think they might "ruin" our breed? Do we think they can't do right by the puppies? Do we not have time and stamina it entails to mentor someone? Actually it is some of all of the above. But truly the bottom line for the breeders I spoke with is "W***ill you be able to do right by the puppies you produce?"*** This is so much more than keeping the pen clean, socializing them, getting the proper shots and worming. Can you screen buyers so the puppies are placed in the right type of home for this breed? Are you willing to spend hours on the phone with folks who have your puppies patiently going over yet again crate training? House training, nipping, barking etc.? Are you willing to take this dog back for any variety of reasons, for his entire life? And I mean entire life! In Schips this might mean easily 15 or 16 years? Will you keep in touch with people (as much as reasonable possible) and monitor the health of the dogs your produce so you might know if you have problems in your line? These are some of the many things responsible, "good" breeders do. Give this some thought before you decide to breed your Schipperke.

This is a special issue, distributed only at the 2008 SCA National Specialty in Tulsa, OK. It also can be found on the Foundation's website. We hope you enjoy it and will contribute generously.

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June Moore
5804 South Hwy 349
Midland, TX 779706-7636

Beverly Henry, Editor
1129 Lake Bluff Drive
Little Elm, Texas 75068

Phone: 972-294-4371
Fax: 972-294-4371
E-mail: chestara@sbcglobal.net

The Schipperke Club of America Rescue & Health Foundation has received an advanced exemption as a 501(c)(3) Charitable Organization under the Internal Revenue Service Code. As a result, your gifts and/or donations for rescue, health research and education now qualify as Tax Deductible Donations. We are appreciative of any gifts and support you can provide in order to continue our programs and research.

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Schip toward the future!

ANNUAL MEETING NOTICE

The second Annual Meeting of the Schipperke Club of America Rescue and Health Foundation will be held on Saturday, March 22, 2008 at the Renaissance Tulsa Hotel and Convention Center, 6808 S. 107th Avenue, Tulsa, OK 74133 in the Madrid Ballroom. The meeting will begin at 2:00 PM or 30 minutes after conclusion of Breed judging, whichever comes first.

Guests are welcome.

Red Coat/Alopecia in the Schipperke Study

The SCA Rescue and Health Foundation is proud to announce that we have chosen this study as our first and have donated $1,000 to the Canine Health Foundation to help fund this study. Our goal is to raise $2,000 more from Schipperke fanciers with their donations in the next 3 months. Please help. Make your tax deductible donations by sending a check made payable to SCA Rescue & Health Foundation with the notation "For Alopecia/Red Coat Project". You will find a donation sheet on page 5 of this newsletter.